PATENT CLAIMS

1. A process for producing parenterally, preferably by injection, administrable microparticles containing a biologically active substance, which process comprises:

a) preparing an aqueous starch solution, comprising starch which has an amylopectin content exceeding 85% by weight, in which the molecular weight of the said amylopectin has been reduced such that at least 80% by weight of the material is within the range of 10-10 000 kDa, and which has an amino acid nitrogen content of less than 50 µg per g dry weight of starch, the starch concentration of the solution being at least 20% by weight,

b) combining the biologically active substance with the starch solution under such conditions that a composition in the form of a solution, emulsion or suspension of said substance in the starch solution is formed,

c) mixing the composition obtained in step b) with an aqueous solution of a polymer having the ability of forming a two-phase aqueous system, thereby forming an emulsion of starch droplets which contain the biologically active substance as an inner phase in an outer phase of said polymer solution,

d) causing or allowing the starch droplets obtained in step c) to gel into starch particles through the natural capacity of the starch to solidify,

e) drying the starch particles, preferably after prior removal of said outer phase through washing, and

f) optionally applying a release-controlling shell of a biocompatible and biodegradable polymer, preferably by air suspension technology, to the dried starch particles.

2. A process according to Claim 1, in which the starch has a purity of at most 20 µg, preferably at most 10 µg, and more preferably at most 5 µg, amino acid nitrogen per g dry weight of starch.

3. A process according to Claim 1 or 2, in which the starch has an amylopectin content with said reduced molecular weight exceeding 95% by weight, preferably exceeding 98% by weight.

4. A process according to claim 1, in which the molecular weight of said amylopectin is reduced such that at least 80% by weight of the material is within the range of 100-4 000 kDa, preferably 200-1 000 kDa, and more preferably 300-600 kDa.

5. A process according to claim 1, in which the starch is such that it can be dissolved in a concentration exceeding 25% by weight in water.

6. A process according to claim 1, in which the starch is essentially lacking in covalently bonded extra chemical groups of the type which are found in hydroxyethyl starch.

7. A process according to claim 1, in which the starch has an endotoxin content of less than 25 EU/g and contains less than 100 microorganisms per gram.

8. A process according to claim 1, in which the starch is essentially purified from surface-localized proteins, lipids and endotoxins by means of washing with aqueous alkali solution, reduced in molecular weight by means of shearing, and purified from internal proteins by means of ion exchange chromatography, preferably anion exchange chromatography.

9. A process according to claim 1, in which in step a) 2-15% by weight amylose is also used as a starch, having an average molecular weight within the range of 2.5-70 kDa, preferably 5-45 kDa, in which the percentage share by weight is calculated on the basis of dry weight

of starch.

10. A process according to claim 1, in which in step a) a solution is prepared having a starch concentration of at least 30% by weight.

11. A process according to claim 1, in which in step a) a solution is prepared having a starch concentration of at most 50% by weight, preferably at most 45% by weight.

12. A process according to claim 1, in which the aqueous starch solution in step a) is prepared with accompanying autoclaving of the same.

13. A process according to claim 1, in which in step b) the active substance is combined with the starch solution at a temperature of at most 60°C, preferably 20-45°C, especially 30-37°C.

14. A process according to claim 1, in which in step b) a composition is formed in which the weight ratio between starch and biologically active substance is within the range of 3:1 to 10 000:1, preferably 3:1 to 100:1.

15. A process according to claim 1, in which in step c) the polymer is used in a concentration in said aqueous solution of at least 20% by weight, preferably at least 30% by weight.

16. A process according to claim 1, in which in step c) the polymer is used in a concentration in said aqueous solution of at most 45% by weight, preferably 30-40% by weight.

17. A process according to claim 1, in which the mixing in step c) is performed at a temperature within the range of 4-50°C, preferably 10-40°C, especially 10-37°C.

18. A process according to claim 1, in which the mixing in step c) is performed with the aid of at least one static mixer.

19. A process according to claim 1, in which in step c) the polymer solution is added to the composition

in at least two steps, in which at least one of the additions is effected after the emulsion has begun to be created.

20. A process according to claim 1, in which in step c) polyethylene glycol is used as the aqueous polymer.

21. A process according to Claim 20, in which the polyethylene glycol has an average molecular weight of 5-35 kDa, preferably 15-25 kDa, especially about 20 kDa.

22. A process according to claim 1, in which the solidification in step d) is performed at at least two temperatures, in which the initiation is effected at a lower temperature than the termination.

23. A process according to Claim 22, in which the solidification is initiated within the range of 1-20°C, preferably 1-10°C, especially around 4°C, and is terminated within the range of 20-55°C, preferably 25-40°C, especially around 37°C.

24. A process according to claim 1, in which the drying in step e) is performed in the form of spray-drying, freeze-drying or vacuum-drying, preferably freeze-drying.

25. A process according to claim 1, in which, as the biologically active substance, a substance is incorporated which is chosen from the group consisting of proteins, peptides, polypeptides, polynucleotides and polysaccharides, especially recombinantly produced proteins.

26. A process according to claim 1, in which said substance is selected from growth factors, insulin, erythropoietin, interferon α, interferon β, interferon γ, blood coagulation factors V, VI, VII, VIII, IX, X, XI, XII and XIII, protein C, glucagon-like peptide 1 or 2, C-peptide, epidermal growth factor, growth hormone, LHRH-analogues, civamide, macrophage colony-stimulating factor,

granulocyte colony-stimulating factor, leptin and interleukin, or an analogue or derivate of any one thereof, which possesses essentially the same pharmacological activity as the parent substance or improved pharmacological activity as compared thereto.

27. A process according to claim 1, in which in step c) starch droplets are formed which give the size required for the microparticles, preferably a mean particle diameter, in the dry state, within the range of 10-200 µm, preferably 20-100 µm, more preferably 20-80 µm.

28. A process according to claim 1, in which after step d) the microparticles are washed, through filtration, and optionally sieved in order to obtain the desired particle size distribution.

29. Microparticles suitable for parenteral administration, preferably via injection, to a mammal, especially a human, and containing a biologically active substance, which microparticles essentially consist of starch having an amylopectin content exceeding 85% by weight, of which at least 80% by weight has an average molecular weight within the range of 10-10 000 kDa and having an amino acid nitrogen content of less than 50 µg per gram dry weight of starch, and which have no covalent chemical cross-linking between the starch molecules.

30. Microparticles according to claim 29, in which the starch is of the kind defined in any one of claims 2-9.

31. Microparticles according to any one of claims 29 and 30, in which the bioactivity of the biological substance is at least 80%, preferably at least 90% and more preferably essentially maintained compared with the bioactivity exhibited by the substance prior to its incorporation in the starch.

32. Microparticles according to claim 29, which are biodegradable in vitro in the presence of alpha-

amylase and/or amyloglucosidase.

33. Microparticles according to claim 29, which are biodegradable and are eliminated from tissue after subcutaneous or intramuscular administration.

34. Microparticles according to claim 29, which have a release-controlling shell of at least one film-forming biocompatible and biodegradable polymer.

35. Microparticles according to Claim 34, in which the polymer is a homopolymer or copolymer containing alpha-hydroxy acid units.

36. Microparticles according to Claim 35, in which the alpha-hydroxy acid is lactic acid and/or glycolic acid.

37. Microparticles according to claim 34, in which said shell contains at least one release regulating substance, in addition to said polymer.

38. Microparticles according to claim 37, in which said substance is water soluble or sparingly water soluble.

39. Microparticles according to claim 38, in which said substance is selected from lactic acid, oligomers containing lactic acid and glycolic acid.

40. Microparticles according to claim 38, in which said substance comprises polyethylene glycol (PEG) or a block copolymer comprising PEG as one of the blocks.

41. Microparticles according to claim 29, which have an outer layer of at least one water soluble substance having the ability to prevent aggregation of the microparticles.

42. Microparticles according to claim 29, which are injectable using a 23 G needle.

43. Microparticles according to claim 42, which are injectable using a 25 G needle.

44. Microparticles according to claim 29, which are injectable through the skin using a dry powder

injection.

45. Microparticles according to claim 29, which are injectable by means of a needle-free injector.

46. Microparticles which are obtainable by means of a process according to claim 1.